REMARKS

Claims 1 and 9 have been amended to include the elements of claims 7 and 8, and three additional adjuvants suitable for human administration disclosed in paragraph 150 or 152. Claims 7, 8 and 14 have been rendered substantially redundant by this amendment and have been cancelled. Withdrawn claims 15-53 have been cancelled. Withdrawn claims 47, 48 and 52 have been amended to refer to claim 1. Applicants now address the Examiner's remarks using the paragraph numbering of the office action.

The objection to claim 14 is moot in view of cancellation of this claim.

35 USC 103

It is believed that all claims currently under examination have priority back to USSN60/137,010, which is solely invented by Dale Schenk. Unless the Examiner disagrees with this analysis, applicant will proceed to file a correction of invention deleting the other named inventor (who contributed to other subject matter not presently being examined).

Claims 1-14 stand rejected as allegedly obvious over Yoshimoto or Wakabyashi in further view of Que and Cleland. Yoshimoto and Wakabayashi are both cited as teaching use of alpha synuclein to raise polyclonal sera. The Examiner acknowledges that these references do not teach an adjuvant or a carrier. Que is cited as teaching use of carriers in vaccines. Cleland is cited as discussing the stability of the adjuvant QS21. The Examiner alleges that one would have been motivated to combine Yoshimoto or Wakabyashi to increase the immune response as well as to ensure a longer shelf life using a stable adjuvant. This rejection is respectfully traversed, particularly insofar as it might be applied to the amended claims.

The Yoshimoto or Wakabyashi papers are both from the same research group and effectively provide the same discussion of using alpha synuclein to generate polyclonal antibodies. Neither paper provides details of the protocols. However, the protocol can be discerned by tracing back through the cited references to Iwai et al., Neuron 14, 467-475 (1995) (copy attached, reference 21 in the Yoshimoto paper). Iwai et al. indicate that polyclonal sera was generated using Freund's adjuvant (complete Freund's adjuvant for first inoculation and

incomplete Freund's adjuvant for subsequent inoculations). According to Harlow & Lane, *Antibodies: A Laboratory Manual* (CSHL 1988)) at p. 98 (copy attached), Freund's adjuvant is the most commonly used for immunization laboratory animals but is too toxic for use in humans.[1]

"To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance,* 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood,* 28 USPQ2d 1300, 1302 (BPAI 1993). Here, it is respectfully submitted that the skilled person would not have been impelled to switch from using Freund's adjuvant to QS21 from the teachings of the cited references. Cleland discusses QS21 in the context of a vaccine for prophylaxis of HIV infection in humans. By contrast, Yoshimoto or Wakabyashi discusses conventional use of alpha synuclein to generate polyclonal sera as a laboratory reagent. Without any discussion of therapeutic implications of immunization of alpha synuclein in any of the cited references, there would have been no reason to think that selection of an adjuvant suitable for human administration would have any advantage in this procedure.

Further, Cleland's discussion of appropriate conditions for formulating QS21 to minimize its degradation in a pharmaceutical product would not have been seen as relevant to use of alpha synuclein to generate polyclonal sera as a laboratory reagent for several reasons. First, it is not known that Freund's adjuvant, the most commonly used laboratory adjuvant, has similar degradation issues to QS21. Thus, the observation that degradation issues of QS21 might be in part overcome by appropriate formulation would not have been seen as an advantage over use of Freund's adjuvant. Second, the needs of stability are different in an HIV vaccine and laboratory immunogen. For an HIV vaccine, the advantages of having a long-shelf life and

[1] Purer forms of incomplete Freund's adjuvant, for example, sold under the trade name of Montanide can be used for administration to humans (see, e.g., Chang, Advanced Drug Delivery Reviews 32, 173-186 (1988) (copy attached). However, there is no indication that Iwai et al. used anything other than a standard laboratory grade.

being in a form that can be administered straight out of the bottle for field use in relatively undeveloped parts of the world having high rates of HIV infection are readily apparent. By contrast, a laboratory would only need to immunize a few times total to generate a sufficient supply of antibodies, and it would have been little trouble for a technician to freshly mix adjuvant with immunogen on each such occasion. Thus, the skilled person would not be greatly concerned about long shelf-life of an adjuvant-antigen formulation and in any event would have no reason to think that that QS21 had meaningfully, if any, better stability than Freund's adjuvant.

For these reasons, it is submitted that the skilled person would not have been impelled to replace the most common laboratory adjuvant, i.e., Freund's adjuvant, with QS21 or other adjuvant suitable for human administration, in a standard procedure for generating a laboratory reagent.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Attachments
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